contacting said antigen presenting cells with naïve T-cells; wherein in response to said peptide, said T-cells proliferate;

(b) modifying said protein to neutralize said T-cell epitope such that the modified protein induces less than or substantially equal the baseline proliferation of said naïve T cells[in a sample].

14. (Once amended) The method according to claim 13, wherein said epitope is modified by:

(a) substituting the amino acid sequence of the epitope with an analogous sequence from a human homolog to the protein of interest;

(b) substituting the amino acid sequence of the epitope with an analogous sequence from a non-human homolog to the protein of interest[, which analogous sequence produces a lesser allergenic response from T-cells than that of the protein of interest]; or

(c) substituting the amino acid sequence of the epitope with a sequence which substantially mimics the major tertiary structure attributes of the epitope[, but which produces a lesser allergenic response from T cells than that of the protein of interest].

REMARKS

The Invention.

This invention provides for methods of obtaining proteins which induce a lower allergenic response in humans exposed to the proteins. Specifically, T-cell epitopes of a precursor protein are altered to produce a protein of lowered allergenicity.

Status of the Application.

Claims 13 and 14 are pending with claims 1-12 and 15 and 16 being canceled with entry of this Preliminary Amendment. The amendment to claim 13 is supported on page 9, line 16, *et seq*. The amendments to claim 14 remove allegedly confusing subject matter. No new matter has been added with these amendments.

Claim 14 stands rejected under 35 USC § 112, second paragraph as allegedly indefinite. Claims 13 and 14 stand rejected under 35 U.S.C. § 102 as allegedly anticipated by US Patent 5,820,862 (the '862 patent) and Felhner, *et al., J. Immunol.* **146**:799 (1991).

Status of the Drawings.

The Applicants acknowledge the filing of informal drawings. Before or concurrent with the payment of an issue Fee, the Applicant will file formal drawings.

Sequence Listing.

Concurrently with this Preliminary Amendment, the Applicants have filed the appropriate Sequence Listing.

Information Disclosure Statement

An Information Disclosure Statement accompanied with a Form 1449 and the listed reference is submitted with this Preliminary Amendment.

35 U.S.C. § 112, Second Paragraph.

Claim 14 stands rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. The Applicants have amended claim 14 to remove the language the Examiner finds confusing. Because claim 14 depends from claim 13, it is clear from the language in claim 13 that the modified epitopes induce less than or substantially equal the baseline proliferation of naïve T cells. In light of the amendments to claim 14, the

Applicants respectfully request the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

35 U.S.C. § 102

Claims 13 and 14 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent 5,820,862 (the '862 patent) and under 35 U.S.C. § 102(b) by Fehlner, *et al., J. Immunol.* **146**:799 (1991).

"A claim is anticipated only if each and every element as set for the in the claim is found, either expressly or inherently described in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987).

In the response to the Office Action dated May 26, 1999, the Applicants argued that claims 13 and 14 were not anticipated because these claims call for a modification of a protein so that a T-cell epitope is neutralized, *i.e.,* peptides derived from the modified protein are not identified by a T cell that recognizes peptides derived from the precursor protein and therefore do not bind to the T cell. For support, the Applicants pointed the Examiner to page 5, line 30 of the instant application. The Examiner responded that he could not find that teaching. The Examiner is correct. On page 5, lines 28-30, the Applicants write: "According to another embodiment of the present invention, a protein is provided in which a T-cell epitope is modified so as to reduce or preferably neutralize (eliminate) the ability of the T-cell to identify that epitope." There is no mention of a T cell not binding to a modified T-cell epitope.

The Applicants have amended claim 13 so that the T-cell epitope to be modified causes the proliferation of naïve T-cells. Neither the '862 patent nor Fehlner, *et al.* contains this element of the claim and therefore they cannot anticipate claims 13 and 14. In light of the amendment to claim 13, the Applicants respectfully request the rejection of claims 13 and 14 on this basis be withdrawn.

In light of the above remarks, the Applicants believe the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early

date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-7609.

Respectfully submitted,

Date: July 12, 2000

Susan Faris
Registration No. 41,739

Genencor International, Inc.
925 Page Mill Road
Palo Alto, CA 94304
Tel: 650-846-7609
Fax: 650-845-6504

Appendix I

13. (Twice amended) A method of reducing the allergenicity of a protein comprising the steps of:

(a) identifying a T-cell epitope in said protein; comprising contacting a peptide comprising said epitope with antigen presenting cells and contacting said antigen presenting cells with naïve T-cells; wherein in response to said peptide, said T-cells proliferate;

(b) modifying said protein to neutralize said T-cell epitope such that the modified protein induces less than or substantially equal the baseline proliferation of said naïve T cells.

14. (Once amended) The method according to claim 13, wherein said epitope is modified by:

(a) substituting the amino acid sequence of the epitope with an analogous sequence from a human homolog to the protein of interest;

(b) substituting the amino acid sequence of the epitope with an analogous sequence from a non-human homolog to the protein of interest; or

(c) substituting the amino acid sequence of the epitope with a sequence which substantially mimics the major tertiary structure attributes of the epitope.